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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,073	11/13/2003	Beth E. Drees	007262-30 US	7922

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,073	DREES ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,10-13,32-34 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,10-13,32-34 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/28/10 has been entered. Currently, claims 1-4, 7, 8, 10-13, 32-34 and 38 are pending and are under examination.

Withdrawn Rejections

In light of the abandonment of Application 10/850,833 by Applicant. The double patenting rejections based on 10/850,833 have been withdrawn.

Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 32-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method of screening a disease caused alteration of a lipid phosphatase comprising the step of using the lipid phosphates assay method of claim 1 to detect changes in the lipid phosphatase activity in bodily tissue, blood or serum samples of a patient with a disease, whereby detection of a change from normal levels indicates a disease caused alteration of a lipid phosphatase. The specification on page 2 under the section entitled background of the invention, the applicant discloses that lipid phosphatases and alterations in their activity levels are implicated in a variety of signaling pathways that are important in regulation of insulin sensitivity and allergic and immune responses, and which are altered in carcinogenesis. The specification on page 8, lines 21-26 discloses that the signaling pathways involving these lipid modifying enzymes are often perturbed in the events leading to disease, particularly in non-insulin dependent diabetes mellitus and cancer. The specification

further discloses that the tools developed in the present invention have significant value for research and in diagnostic applications. The specification on page 9, lines 27-29 discloses that the lipid phosphatase assay is a screening method for disease detection, i.e. Cowden's disease, and a molecule for treating such disease by detection of alteration of lipid phosphatase activity. The specification on page 10, lines 13-15 discloses that the lipid phosphatase assay can be used as a screening method for detection of a disease by detection of a predetermined level of the $PI(3,4)P_2$ or $PI(4,5)P_2$ lipid. The applicant has not disclosed how one skilled in the art can use just single determination of a change of lipid phosphatase activity and have it correlated with only disease. The specification does not provide working examples, controls or standards or guidance on how a change in lipid phosphatase indicates only disease caused alteration of a lipid phosphatase. Komazawa et al (Nature Medicine, Vol 10, No. 11, 2004, pgs 1208-1215) teaches that the expression levels of PTEN protein (lipid phosphatase) are significantly increased in obesity (e.g. abstract, p. 1211) and decreased in exposure to cold (abstract, p. 1211). Bhashyam et al., (Am J Physiol Heart Circ Physiol, Vol 293 pgs H3063 –H3071) teaches the increased expression of PTEN (lipid phosphatase) in cardiac muscle in older dogs but not in skeletal muscle (e.g. p. H3067) Bhashyam et al also teaches that increased PTEN (lipid phosphatase) activity in the hearts of young dogs with dilated cardiomyopathy (e.g. p. H3068). Further, it is unclear if the change of activity involves both increases and decreases of lipid phosphatase is indicative of a disease caused alteration of a lipid phosphatase. The specification on page 4, lines 1-2 disclose that ablation of SHIP1 in transgenic mice

leads to chronic hyperplasia and increased proliferation and survival of hematopoetic cells. One of ordinary skill in the art would understand that this is a decreased lipid phosphatase activity. The specification on page 4, lines 33-34 discloses that a loss of PTEN activity results in accumulation of $PI(3,4,5)P_3$. Thus, it appears that only decreases of lipid phosphatase may be correlated with disease. However, the specification does not provide for differentiating lipid phosphatase activity in disease from that of age, temperature or obesity. Such is not seen as sufficient to support the breath of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because in order to establish if the lipid phosphatase activity indicates a disease caused alteration of lipid phosphatase, one skilled in the art would not be able to differentiate if the lipid phosphatase alteration is caused by obesity, age, temperature or disease, and one skilled would not have a high level of predictability.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-4, 7, 10, 11, 32-34 and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Dowler et al (WO 02/12276).

Dowler et al disclose methods for detecting or quantifying enzyme activity such as lipid phosphatases (p. 34 & pages 130-135). Dowler et al disclose exposing a

protein (lipid detector protein) that binds specifically to product lipids. Dowler et al discloses that the protein comprise a PH domain (lipid recognition motif) which is specific for product lipids (p. 130). Dowler et al disclose exposing the protein (lipid detector protein) comprising the PH domain to substrate lipid and sample and determining if the protein bound to a product lipid. Dowler et al disclose that the PH domain may be in the form of a fusion protein or that the PH domain may be tagged (p.130 & p.132). Dowler et al disclose that the method can comprise the substrate lipid in free solution (p. 133-134). Dowler et al disclose that prior to contacting that a microtiter plate surface can be coated with lipid substrate that comprises a chromophore (p. 131). Dowler et al disclose that the method may be used for making real time measurement throughout the course of the reaction (p. 132, lines 12-20). Dowler et al disclose that a FRET assay (fluorgenic assay) can be used to determine the enzyme activity. Dowler et al disclose that the substrate lipid can be immobilized or free in solution. Dowler et al disclose that the substrate lipids can be $PI(3,4,5)P_3$ or $PI(4,5)P_2$ and the product lipid PI(4)P (p. 131). Dowler et al disclose that the method may be used to identify modulators of lipid phosphatase activity (p. 34, lines 21-28) by measuring lipid phosphatase activity in the presence and absence of a compound. Dowler et al discloses that the sample can be from a diseased patient.

With respect to the recitation "wherein a change in concentration for any of the above substances between steps (a) and (b) indicates that said product lipid is present in said solution". Dowler et al teaches determining the level of activity and teaches the method may be used in real time measurement throughout the course of the reaction

and it is inherent that when the enzyme activity reacts upon the substrate lipid that there is an increase in the amount of product lipid in the assay. Thus, Dowler et al reads on the instantly recited claim.

With respect to claim 32 as instantly recited. The recitation "to detect changes in the lipid phasphatase activity" are intended use of the method of claim 1 and since Dowler et al teaches every active method step of claim 1. Dowler et al reads on claim 32. Regarding the interpretive "whereby" clause recited in claim 32 ("whereby detection of a change from normal levels indicates a disease caused alteration of a lipid phosphatase", the clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results to those steps. Therefore, the "whereby" clause is not considered to further limit the method defined by the claim and has not been given weight in construing the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A whereby clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dowler et al (WO 02/12276) in view of Goueli et al (US 6,720,162).

See above for the teachings of Dowler et al.

Dowler et al differ from the instant invention in failing to teach the plate is coated with streptavidin.

Goueli et al teaches method for determining lipid phosphatase activity. Goueli et al disclose coating a plate with streptavidin used in assays for lipid phosphatase activity (col 3 & col 9). Goueli et al disclose that this provides for an easy means to separate the products of an enzymatic reaction from unreacted reactant, enzyme and other nonproduct ingredients of a reaction solution (col 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate coated streptavidin and biotin systems as taught by Goueli et al into the methods of Dowler et al because Goueli et al teaches that this provides for an easy means to separate the products of an enzymatic reaction from unreacted reactant, enzyme and other nonproduct ingredients of a reaction solution. Further, the use of streptavidin to immobilize reactants of assays is very well known in the art.

10. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dowler et al in view of Taylor et al (Analytical Biochemistry, 295, 122-126, 2001).

See above for the teachings of Dowler et al.

Dowler et al differs from the instant invention in failing to teach the lipid phosphatase is myotubularin or PTEN. Dowler et al also fails to specifically state that the sample has additional lipids.

Taylor et al disclose assays for determining phosphoinositide phosphatases such as myotubularin and PTEN which act on phosphoitidylinositol phosphates in samples . Taylor et al disclose that the sample can have different lipids. Taylor et al teaches that

these enzymes are studied to better understand their role in the synthesis, breakdown, and interconversion of inositiol lipids.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate or determine myotubularin and PTEN activity as taught by Taylor et al into the method of Dowler et al because Dowler et al is generic with respect to the lipid phosphatases to be determined and Taylor et al teaches that the determination of myotubularin and PTEN which act on phosphoitidylinositol phosphates in samples provides for a better understanding of their role in the synthesis, breakdown, and interconversion of inositiol lipids.

Response to Arguments

11. Applicant's arguments filed 07/07/09 have been fully considered but they are not persuasive.

112 first paragraph rejections

Applicant argues that the instant specification provides sufficient examples and guidance related to provide a high level of predictability that the lipid phosphatase activity indicates a disease-caused alteration. The Applicant directs the Examiner's attention to Table 1 and paragraphs 0016 to 0018. This is not found persuasive because the table does not provide for normal levels (as recited in the claims) or increases or decreases compared to normal levels nor does the Applicant provide any working examples or guidance on what is considered to be normal. As stated above and in the previous office actions the applicant has not disclosed how one skilled in the

art can use just single determination of a change of lipid phosphatase activity obtaining from any patient and have it correlated with only disease. The specification does not provide working examples, controls or standards or guidance on how a change in lipid phosphatase indicates only disease caused alteration of a lipid phosphatase.

The Applicant also states that the changes associated with disease would be much greater than that associated with obesity, age, temperature or disease and that one skill in the art would appreciate this distinction when reviewing assay results. This is not found persuasive because the Applicant has not provided factual evidence showing that the levels or activity in disease are much greater than that associated with obesity, age or temperature. Applicant is also reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) (see MPEP 716.01(c) & MPEP 2145).

102 rejections

Applicant argues that the Dowler reference teaches a method where a substrate lipid is incubated with an appropriate enzyme in the presence of a PH domain fused green fluorescent protein (applicant directs Examiners attention to p. 131, lines 24-28). Applicant further states that Dowler does not disclose exposing a lipid detector protein to a solution containing a substrate lipid and lipid phosphatase.

This is not found persuasive because the Examiner has not relied upon the section of page 131, lines 24-28 solely (see rejections above and in previous office actions). Also, one of ordinary skill in the art must consider all embodiments of a

disclosure. Further, it is well settled that a reference must be evaluated for all disclosures not just its preferred embodiments. *In re Mills,* 470 F. 2d 649, 176 USPQ 196 (CCPA 1972). As stated above Dowler et al disclose exposing a protein (lipid detector protein) that binds specifically to product lipids. Dowler et al discloses that the protein comprise a PH domain (lipid recognition motif) which is specific for product lipids (p. 130). Dowler et al disclose exposing the protein (lipid detector protein) comprising the PH domain to substrate lipid and sample and determining if the protein bound to a product lipid. Dowler et al disclose that the PH domain may be in the form of a fusion protein or that the PH domain may be tagged (p.130 & p.132). Dowler et al disclose that the method can comprise the substrate lipid in free solution (p. 133-134). Dowler et al disclose that prior to contacting that a microtiter plate surface can be coated with lipid substrate that comprises a chromophore (p. 131). Dowler et al disclose that the method may be used for making real time measurement throughout the course of the reaction (p. 132, lines 12-20). Dowler et al disclose that a FRET assay (fluorgenic assay) can be used to determine the enzyme activity. Dowler et al disclose that the substrate lipid can be immobilized or free in solution. Dowler et al disclose that the substrate lipids can be $PI(3,4,5)P_3$ or $PI(4,5)P_2$ and the product lipid PI(4)P (p. 131).

With respect to Applicant's argument that Dowler does not disclose a solution containing a substrate lipid and lipid phosphatase. It is noted that nowhere in the instant claim is it recited that a solution contains a substrate lipid and lipid phosphatase. Further, one of ordinary skill in the art would recognize that in the assay of Dowler (described supra) that the substrate and enzyme present cause the conversion of the

substrate into lipid products (see e.g. pgs. 131 & 133-134). Therefore, the substrate lipid and lipid phosphatase much be present together for the conversion into lipid products.

Applicant argues that Dowler does not mention PI(4,5)P2, or PI and specifically does not disclose binding of PI(3,4,5)P3.

This is not found persuasive because as stated above and in the previous office actions Dowler specifically teaches the substrate lipids can be PI(3,4,5)P3 or PI(4,5)P2 (p. 131 Dowler). Further, with respect to the binding of PI(3,4,5)P3 as currently argued by the Applicant. It is noted that binding to the PI(3,4,5)P3 is not recited in the current claims.

Applicant further argues that Dowler does not disclose determining the levels of a substrate lipid, lipid detector protein and lipid product in solution. This is not found persuasive because the currently recited claim does not recite determining the levels of substrate lipid, lipid detector protein and lipid product in solution. The instant claim recites "determining a change in concentration of at least one of the following: substrate lipid, lipid detector protein and lipid product" and Dowler reads on this limitation for the reasons stated above and in the previous office actions.

103 rejections

Applicant argues that the Examiner has mischaracterized Goueli and states that the Goueli reference described lipid kinase and phosphatase assays where the lipid kinase and phosphatase assays where the lipid substrate is modified, i.e. biotinylated or

immobilized and is detected radioactively which requires a separation step. The liquid phase assay in the Goueli column 3 is also liquid during the enzymatic conversion, but detection still requires radioactivity and separation. The applicant argues that the claimed lipid phosphase assay always detect the lipid product, use nonbiotinylated/mobile substrate and do no require radioactivity.

This is not found persuasive because the instantly recited claims do not recite nonbiotinylated/mobile substrate and do not exclude the use of radioactivity. Further, the Examiner has not relied upon Goueli for teaching the recited method but rather has relied upon Goueli for teaching that it is known and conventional in the art to incorporate streptavidin and biotin systems into assays and for teaching the advantages of using such a system and since Goueli teaches analogous art and the advantages of using such systems one or ordinary skill in the art would be motivated to incorporate such systems into the method of Dowler et al and one would also have a reasonable expectation of success.

Applicant further appears to argue that the reference of Taylor fails to cure the deficiencies of the Dowler reference. This is not found persuasive because of reasons stated above that Dowler reads on the instantly recited claims. Thus, the combination of Dowler and Taylor et al is considered appropriate and still reads on the instantly recited claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641